

I. STUDIES OF THE SYNTHESIS OF A THIOPHENE
ANALOG OF INDOLE

II. A NEW SYNTHESIS OF INDOLE-3-ALDEHYDE

BY

SAMBASIVA SWAMINATHAN

B.Sc.(Hons.), Annamalai University, 1943

M.A., Annamalai University, 1945

A.I.I.Sc., Indian Institute of Science, 1946

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SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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I. STUDIES OF THE SYNTHESIS OF A THIOPHENE ANALOG OF INDOLE

INTRODUCTION

Recent studies¹ have shown that the substitution of one by the other of the isosteric groups -O-, -NH-, -S- and -CH = CH- in the structure of an essential amino acid often results in a compound which inhibits or interferes with the metabolic activity of the particular amino acid. Such compounds are of interest as potential antibacterial agents.

With a view to the preparation, ultimately, of an analog of tryptophan, the synthesis of thiopheno-2,3:2',3'-pyrrole, a thiophene analog of indole, and derivatives thereof has been studied.

DISCUSSION OF RESULTS

2-Acetamido-3-methylthiophene and 2-benzamido-3-methylthiophene were prepared *via* the sequence: 3-methylthiophene, 2-nitro-3-methylthiophene, 2-amino-3-methylthiophene, 2-acetamido (or benzamido)-3-methylthiophene. 2-Acetamido-3-methylthiophene was also obtained by the Beckmann rearrangement of the oxime of 2-acetyl-3-methylthiophene. Treatment of 2-acetamido-3-methylthiophene and 2-benzamido-3-methylthiophene with sodium amide and potassium tertiary butoxide did not yield the desired indole.

The applicability of the method² whereby phenacylaryl-anilines are converted to substituted indoles has been examined. 2-Phenacylaminothiophene was obtained *via* the sequence: 2-nitrothiophene, 2-aminothiophene, 2-acetamidothiophene, N-acetyl-N-phenacyl-2-aminothiophene, phenacylaminothiophene. Neither 2-phenacylaminothiophene nor N-acetyl-N-phenacyl-2-aminothiophene would indolize under the conditions which have been used for the indolization of phenacylaryl-anilines.

The preparation of 2-nitro-3-thenyl cyanide was undertaken with a view to the application of Stephen's method³ of ring closure. 2-Nitro-3-thenyl bromide, obtained by nitration of 3-thenyl bromide, failed to yield the corresponding cyanide. Triethyl-2-nitro-3-thenylammonium bromide, prepared by reacting 2-nitro-3-thenyl bromide with triethylamine, also failed to yield the desired cyanide when treated with sodium cyanide. Alternatively, the preparation of 2-nitro-3-thenyl cyanide was attempted by nitration of 3-thenyl cyanide, which was obtained by reacting 3-thenyl bromide with sodium cyanide. A mixture, probably of 2 and 5-nitro-3-thenyl cyanides, was obtained, but was not converted into the desired indole on treatment with stannous chloride. 2-Nitro-3-thenaldehyde was prepared by the application of Sommelet's method to 2-nitro-3-thenyl bromide.

The last scheme, which proved to be the most promising, was as follows: 3-methylthiophene, 2-nitro-3-methylthiophene, dimethyl-*beta*-(2-nitro-3-thienyl)ethylamine, 4',5'-dihydro-thiopheno-2,3:2',3'-pyrrole, thiopheno-2,3:2',3'-pyrrole. Dimethyl-*beta*-(2-nitro-3-thienyl)ethylamine was prepared by reacting 2-nitro-3-methylthiophene with formaldehyde and dimethylamine. Its structure was proved by synthesis as follows: 3-methylthiophene, 3-thenyl bromide, 3-thienylacetic acid, *beta*-3-thienylethyl alcohol, *beta*-3-thienylethyl bromide, *beta*-(2-nitro-3-thienyl)ethyl bromide, dimethyl-*beta*-(2-nitro-3-thienyl)-ethylamine. The same tertiary amine was reduced to a compound, possibly 4',5'-dihydro-thiopheno-2,3:2',3'-pyrrole or 2-amino-3-ethylthiophene. The reduction product on dehydrogenation with sulfur was converted to a new compound, possibly thiopheno-2,3:2',3'-pyrrole.

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II. A NEW SYNTHESIS OF INDOLE-3-ALDEHYDE

INTRODUCTION

A large number of amines prepared by the Mannich reaction contain labile amino groups and react with primary and secondary amines by a process of 'amine exchange'¹. It was considered likely that such a reactive Mannich base, either in acid solution or in the form of its quaternary salt might undergo an amine exchange with hexamethylenetetramine. The product would be a quaternary salt of hexamethylenetetramine of the type encountered in Sommelet's synthesis² of aldehydes and might decompose to give an aldehyde.

The present work is concerned with a study of the reaction between hexamethylenetetramine and reactive Mannich bases, like gramine, to give aldehydes.

DISCUSSION OF RESULTS

Indole-3-aldehyde has been prepared by reacting gramine-(3-dimethylaminomethylindole) with hexamethylenetetramine in glacial acetic acid.

The reaction of certain Mannich bases derived from heterocyclic compounds, ketones and phenols with hexamethylenetetramine has been studied. The Mannich bases containing the dimethylaminomethyl group and derived from 2-carbethoxyindole, phenol and *beta*-naphthol have been converted into 2-carbethoxyindole-3-aldehyde, salicylaldehyde and 2-hydroxy-1-naphthaldehyde respectively by reaction with hexamethylenetetramine. A preliminary experiment has indicated the conversion of 1-methylgramine into an aldehyde, probably 1-methylindole-3-aldehyde. The attempts to convert the dimethylaminomethyl Mannich bases of acetophenone, pyrrole and 2-nitro-3-methylthiophene into the corresponding aldehydes failed.

Benzylamine and N-methylbenzylamine reacted with hexa-

methylenetetramine to give benzaldehyde. Benzyldimethylamine, under the same conditions did not yield benzaldehyde.

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VITA

The author was born in Mylapore, Madras, India on April 20, 1923. He graduated from S. M. Hindu High School, Shiyali, Madras, in 1938. The same year he entered Annamalai University from which institution he received the degrees of Bachelor of Sciences (Hons.) in 1943 and Master of Arts in 1945. He was awarded a scholarship by the Madras Government in 1943 and another by the Lady Tata Memorial Trust in 1946 for graduate studies at the Indian Institute of Science, Bangalore. He received the Associateship of the Indian Institute of Science in 1946 for research on sulfanilamide and antipyretic drugs. He was awarded a scholarship by the Government of India for study in the U. S. in 1946. He entered the Graduate College of the University of Illinois in June, 1947.



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